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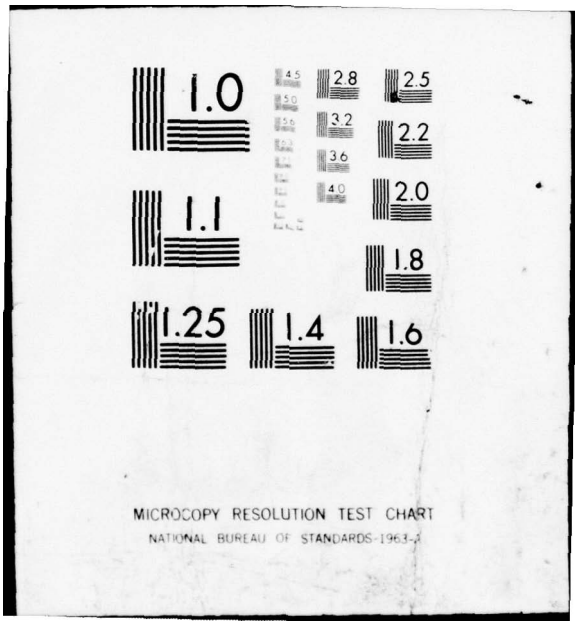
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We have previously demonstrated that the magnitude of post exertional asthma is proportional to the heat exchange that occurs within the airways. Since the level of ventilation is an important determinant of the quantity of heat transferred from the mucosa, we reasoned that if we simulated the hyperpnea of exercise by hyperventilation, we could produce heat exchange similar to that seen with exercise, and thus equivalent bronchial obstruction. To test this hypothesis, we had 8 asthmatics perform eucapnic hyperventilation to mean levels of 63 and 44 L/min while they breathed dry air at subfreezing (-12°C) and room

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temperature (23°C) and fully saturated air at room and body temperature through a heat exchanger in a random order. Multiple aspects of pulmonary mechanics were measured before and after each challenge. Hyperventilation at body conditions (0 heat flux) did not result in any change in pulmonary mechanics. However, as the water content and temperature of the inspirate were decreased, thus increasing the thermal burden on the airways at maximal ventilation ($\dot{V}_E$), the bronchospastic response progressively increased. Decreasing the thermal burden by decreasing V_E proportionally reduced the response. From this we conclude that the major stimulus for exercise-induced asthma is heat loss from the mucosa with subsequent cooling, which is preciptated by the hyperpnea of exercise but not exercise per se.

HYPERPNEA AND HEAT FLUX. THE INITIAL REACTION SEQUENCE IN EXERCISE-INDUCED ASTHMA

Running Title: Hyperpnea, Heat Flux and Asthma

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ABSTRACT

It was

~~We have~~ previously demonstrated that the magnitude of post exertional asthma is proportional to the heat exchange that occurs within the airways. Since the level of ventilation is an important determinant of the quantity of heat transferred from the mucosa, it was ~~we~~ reasoned that if we simulated the hyperpnea of exercise by hyperventilation, ~~we could produce~~ would be produced heat exchange similar to that seen with exercise, and thus equivalent bronchial obstruction. To test this hypothesis, ~~we had~~ 8 asthmatics performed eucapnic hyperventilation to mean levels of 63 and 44 L/min while they breathed dry air at subfreezing (-12°C) and room temperature (23°C) and fully saturated air at room and body temperature through a heat exchanger in a random order. Multiple aspects of pulmonary mechanics were measured before and after each challenge. Hyperventilation at body conditions (0 heat flux) did not result in any change in pulmonary mechanics. However, as the water content and temperature of the inspirate were decreased, thus increasing the thermal burden on the airways at maximal ventilation ($\dot{V}_E$), the bronchospastic response progressively increased. Decreasing the thermal burden by decreasing $\dot{V}_E$ proportionally reduced the response. From this we conclude that the major stimulus for exercise-induced asthma is heat loss from the mucosa with subsequent cooling, which is precipitated by the hyperpnea of exercise but not exercise per se.

V sub E

INTRODUCTION

In previous publications, we have demonstrated that the severity of the airway obstruction that follows physical exertion in asthmatics could be amplified or attenuated in a highly reproducible fashion by raising or lowering the temperature and water content respectively of the inspired air (1-4). From these observations, we deduced that the phenomenon of exercise induced asthma is a function of the heat exchange that takes place within the ajrways during exercise, and have developed quantitative expressions that relate these two events (3,4).

The factors involved in respiratory heat exchange can be expressed by the following equation:

$$RHE = \dot{V}_E [Hc (Ti-Te) + Hv (Wi-We)]$$

where RHE = Respiratory heat exchange (Kcal/min)

$\dot{V}_E$ = minute ventialtion (L/min; BTPS)

Hc = heat capacity of air (specific heat·density) = 0.000304 Kcal/L/^oC

Ti = inspired air temperature (^oC)

Te = expired air temperature (^oC)

Hv = heat of vaporization of H_2O = 0.58 Kcal/g

Wi = water content of the inspired air (mgH_2O/L air)

We = water content of expired air (mgH_2O/L air)

Using this equation it can be readily seen that the lower the values are for Ti and/or Wi, the greater the heat exchange will be for any given $\dot{V}_E$. Conversely, increasing Ti and Wi will result in low heat exchange. Analysis of our previous observations in this context demonstrated that

there was a highly significant, direct, linear relationship between RHE during exercise and the magnitude of the subsequent mechanical response (4). Further, given the absolute values of the constants, Hc and Hv, it is apparent that the most significant heat loss, and therefore, post-exercise response, should result from the vaporization of water. This too has been verified experimentally (3).

It is also clear from the above expression that if the level of ventilation were altered at any given inspired air conditions of Ti and Wi, RHE will change proportionally and so then should the degree of airway obstruction. Obviously, if this were true, then exercise per se should not be a necessary ingredient for the production of exercise-induced asthma, and it should be possible to evoke the syndrome by having the subjects hyperventilate. We have tested this hypothesis in asymptomatic asthmatics, and our results form the basis of this report.

METHODS

Our subjects consisted of 8 atopic asymptomatic asthmatic volunteers with reproducible exercise-induced asthma that had been extensively documented in our laboratory. The mean age of the group was 23.6 ± 1.9 (SD) and all met the American Thoracic Society's definition of asthma (5). None of our subjects smoked, and none had used glucocorticoids or cromolyn sodium for at least 4 weeks before any study day. All refrained from taking any medication for 12 hours prior to any investigation. Informed consent was obtained from each participant.

The measures of pulmonary mechanics that were employed consisted of lung volumes, specific conductance and maximum forced exhalation.

Total lung capacity and its subdivisions and airway resistance were measured in a constant volume variable pressure plethysmograph (Warren E. Collins Co., Braintree, MA.) that was serially interfaced to an analog recorder (Electronics for Medicine, White Plains, N.Y.) and a minicomputer (Lab 8E, Digital Equipment Corp., Maynard, MA.) (6-8). Airway resistance was expressed as a conductance volume ratio termed specific conductance (SGaw) (9). Five measurements of each variable were routinely obtained and the mean computed. These data were considered acceptable if their coefficients of variation were 5% or less. Spirometry was performed in triplicate using a waterless spirometer (Electro Med. Model 780, Searle Cardio-Pulmonary, G.D. Searle and Co., Houston, Texas). One second forced expiratory volumes (FEV_1) were computed by standard techniques. The subject's best effort as defined by the curve with the largest vital capacity and FEV_1 was used for analysis.

We asked our subjects to hyperventilate to levels usually observed with a moderately heavy work load (60-65 L/min) while they inspired dry air at subfreezing and room temperatures, and fully saturated air at room and body temperatures in a random fashion. On another occasion the entire study (with the exception of the body temperature saturated conditions) was repeated at a lower level of $\dot{V}_E$ to simulate a smaller work load. The experimental set-up is shown schematically in Figure 1.

The temperature and water content of the inspired air was controlled by having the subjects breathe through a heat exchanger in series with a bubble humidifier as previously described (3). This instrument complex was capable of producing inspired air temperatures between -15°C and 120°C with relative humidities (RH) varying from zero to 100%.

The temperature of the inspired air was continuously recorded in all experiments by a thermocouple situated in the airstream within the exchanger and located 10 cm upstream from the mouthpiece. Expired air temperature was also measured with a second thermocouple that protruded through the mouthpiece 5 cm into the oral cavity. This thermocouple was shielded so as not to touch any mucosal surface. Expired gas was directed away from the exchanger through a one-way valve into a 7 liter reservoir balloon that was being constantly evacuated through a calibrated rotameter by a vacuum pump. The subjects were instructed to respire in such a fashion so as to keep the reservoir filled, and in so doing their expired $\dot{V}_E$ precisely matched the rate of emptying of the balloon. This method of controlling $\dot{V}_E$ represents a modification of previous techniques that we have employed (10). End-tidal carbon dioxide tensions ($PetCO_2$) were continuously recorded at the mouth by a Beckman LB-2 analyser (Beckman Instruments Inc., Fullerton, California), and displayed on the oscilliscope of the analog recorder. At the inspiratory port of the exchanger a mixing valve permitted us to supply sufficient carbon dioxide to keep $PetCO_2$ constant at resting eucapnic levels and thus avoid the bronchoconstrictive effects of hypocapnia (11).

The water content of the air supplied to the subjects was verified by drawing a known volume of air through glass drying tubes containing anhydrous calcium sulfate (W. A. Hammond Drierite Co., Xenia, Ohio) as previously described (3). Compressed air served as the source of dry air. Pulmonary mechanics were measured before and 5 to 10 minutes after cessation of hyperventilation. In each experiment the air at

various conditions was inhaled for 4 minutes before, during, and for 4 minutes after cessation of hyperpnea. The duration and magnitude of the hyperventilation was kept constant for each subject for each experiment. The period of time the subjects spent hyperventilating corresponded to the time spent performing exhausting leg work in previous studies (1-4, 12). Upon completion of each experiment, the subjects rested for at least one and one-half hours while pulmonary mechanics returned to pre-hyperventilation levels before subsequent challenges were undertaken on any study day. These protocols exactly match those we have routinely employed for exercise provocation of asthma except that eucapnic hyperventilation has been substituted as the stimulus (1-4, 12-15). The data were analyzed by paired t tests and one and two factor analyses of variance.

RESULTS

Table 1 contains the individual values for $\dot{V}_E$, Ti, Wi and $PetCO_2$ for the four hyperventilation experiments that simulated a heavy workload. In these studies the mean value for $\dot{V}_E$ was held constant at approximately 63 L/min, and there were no significant difference in this variable between the four trials ($F=0.93$; $df=3.31$; p NS). In order to vary the thermal burden imposed upon the airways and thus RHE, a wide renge of inspired air conditions was employed, i.e., subfreezing, ambient room temperature with 0% relative humidity; room temperature at 100% relative humidity; and body conditions. End-tidal carbon dioxide tensions ranged between a mean of 36.4 ± 1.3 and 37.7 ± 0.7 mm Hg, and were kept constant at eucapnic levels for all studies ($F = 1.16$; p ns).

The data for the simulation of a moderate work load are shown in Table 2. In this instance $\dot{V}_E$ averaged approximately 44 L/min, and again

there were no significant differences between trials by factorial analysis ($F=0.02$; p NS). As before, $PetCO_2$ was kept at normal resting levels for all studies. There were no significant differences for this variable, nor for Ti or Wi, between the moderate and heavy work load simulation experiments.

Eucapnic hyperventilation at 63 L/min produced significant alterations in SGaw, FEV_1 and RV as measured by baseline response comparisons at all inspired air conditions save for the body temperature, fully saturated experiment (Tables 3 and 4). In the latter study (Table 4) airway obstruction did not develop following hyperventilation, and none of the variables changed from their control values. When the subfreezing and room temperature experiments at 0 and 100% relative humidity were repeated at 44 L/min airway obstruction still developed (Table 5). When fully saturated air at room temperature was inhaled at this $\dot{V}_E$ the changes from control were quite small, and those that occurred in RV did not reach statistical significance.

Comparison of the derangements in pulmonary function that developed with each inspired gas condition as a function of $\dot{V}_E$ revealed a dose-response relationship for each indeed measured (Figures 2, 3 and 4). Hyperventilation at 63 L/min while breathing subfreezing air resulted in considerable obstruction. One second forced expiratory volume, as a representative variable (Figure 2) fell a mean of 39.1% from its control value ($p < 0.001$; Table 3). Decreasing the heat exchange by increasing the inspired air temperature to 23°C significantly reduced the magnitude of the response in that FEV_1 now only fell 28.3%. Further decreasing the heat exchange by saturating the air at 23°C further blunted the response; now FEV_1 changed 11.3% from baseline. Hyperventilation with zero heat exchange (body temperature saturated air) was without effect on lung function. Each of

changes was different from the others at the 0.001 level despite the fact that $\dot{V}_E$ was held constant, and each compared quite favorably to those seen following cycle ergometery while inhaling these air mixtures (1,3,4).

When $\dot{V}_E$ was reduced, the degree of obstruction fell commensurately. The changes that followed hyperventilation while breathing the gas mixtures that produced alterations in mechanics were significantly less at 44 L/min than at 63 L/min. For example, the mean reduction in FEV_1 while inhaling subfreezing air at 44 L/min was 16.2 ± 3.7 (SEM)% versus 39.1 ± 4.8% at 63 L/min ($p < 0.001$). Similar patterns existed for the other air conditions and for SGaw (Figure 3) and RV (Figure 4).

DISCUSSION

In previous studies we have presented evidence that there was a cause and effect relationship between the magnitude of the respiratory heat exchange that occurs during exercise in asthmatics, and the magnitude of the post-exertional obstruction that subsequently develops (3,4). The current work extends these observations by demonstrating that equivalent airway obstruction can be induced by having asthmatic subjects perform eucapnic hyperventilation under conditions that simulate the heat exchange seen with exercise. From this we conclude that the major stimulus for exercise-induced asthma is heat loss from the airway mucosa with subsequent cooling, which is precipitated by the hyperpnea of exercise.

These findings are of considerable interest and serve to eliminate the need to search for humoral substances being released from the working muscles. From this study the role of exercise can be viewed as only the means to increase RHE through hyperpnea. Further, and perhaps more importantly, our findings allow a unifying approach to a variety of perplexing issues, and apparently conflicting results, appearing in the literature

from this and other laboratories.

With respect to our own efforts on the comparison of the relative asthmogenicity of exercise with different muscle groups, we have shown that when dientical physical work loads were applied to the arm and legs, arm exercise resulted in significantly greater airway obstruction, hydrogen ion concentration (H^+), and $\dot{V}_E$ than did the equivalent leg work [12]. The key factor in this study can now be seen to be the fact that $\dot{V}_E$, and thus RHE, was twice as great with arm work. Similarly our investigation on the effects of hydrogen ion, lactic acidosis and the mechanical effects of bulk airflow on airway function can now also be put into perspective [10,12].

Many investigations have noted a temporal association between increases in H^+ concentrations with exercise, and the development of acute exacerbations of asthma (13, 16-25), and this has prompted the speculation of a cause and effect relationship (16). In light of the present study it seems highly likely that the relationship between the severity of the obstruction and the elevation in circulating lactate and/or H^+ is due to the fact that as metabolism shifts from aerobic to anerobic with exercise with release of acid-end products, there is an associated elevation in $\dot{V}_E$ disproportionate to the increment in oxygen consumption. In these circumstances, as $\dot{V}_E$ increases so does RHE, and consequently there is a larger response. Recent evidence has shown that acidemia <u>per se</u> is not the mechanism for exercise-induced asthma since prevention of the rise in H^+ by infusing bicarbonate during exercise does not influence the response [12]. It is of note that in these experiments bicarbonate administration did not alter $\dot{V}_E$ [12] and it would be expected that if $\dot{V}_E$ were to be reduced at a given work load, RHE would fall, and so then should the degree of obstruction.

In an earlier publication that evaluated the relative contributions of hypercarbia and hyperpnea as mechanisms in postexercise asthma, we have demonstrated that the act of achieving and sustaining high $\dot{V}_E$ does not evoke changes in pulmonary mechanics in asthmatics (10). At first examination these findings seem to be at variance with those of the current work , but this apparent incompatability can be readily reconciled. In the previous study eucapnic hyperventilation was achieved by having the subjects rebreathe expired air through a 7.0 litre deadspace into which a small amount of fresh air was entrained by a bias flow to provide adequate alveolar ventilation (10,26). Thus, this arrangement created the situation in which the subjects were inhaling hot wet air that was close to body conditions during the experiments. This fact was recognized at the time, but its true significance was not appreciated. However, it is now clearly established that this inspired gas condition will totally prevent acute exacerbations of asthma from developing either after exercise (3) or eucapnic hyperpnea because of the low thermal burden that it places on the airways (3,4).

The hyperpnea-heat flux hypothesis of exercise-induced asthma also offers at least a partial explanation for those studies that have implicated an increase in bulk air flow as the major stimulus for the induction of bronchospasm in exercise-induced asthma (18,22,25,27-30), and the controversy that they evoked (10,24,31-35). The data in Figures 2 through 4 demonstrate that the variables that are the most important in determining the severity of the response are the absolute level of $\dot{V}_E$ and the temperature and humidity of the inspired air. It is possible that there may be

a level of $\dot{V}_E$ which must be exceeded before a response can be detected utilizing present measures, and that this value changes as inspired air temperature and/or water content increases. For example, using FEV_1 it would require a combination of a $\dot{V}_E$ of 42 L/min and an inspired air temperature of -12°C to cause this variable to fall 15% from its control value (Figure 2), a change frequently arbitrarily chosen to define a response. To produce this same effect with room air (23°C) at the extremes of humidity of 0 and 100%, $\dot{V}_E$ would have to increase approximately 25 and 75% respectively. Since ambient room temperature and humidity are not usually rigorously controlled in most laboratories, and can vary considerably according to season, climate, the type of heating system employed and whether or not air-conditioning is used, it is not difficult to appreciate that considerable variations in response could develop in hyperventilation experiments and this factor could therefore lead to different conclusions. The same phenomenon is operational in exercise challenges as well, and may account for much of the variability that has been reported in studies concerned with the reproducibility of exercise-induced asthma (14,21,36-39),its prevalence in the general asthmatic population (14,36,40), and the observed differences in the relative effectiveness with which stimuli such as swimming and running evoke acute exacerbations (41).

Although it is clear that RHE and airway obstruction are causally related in asthmatics, the exact way in which the stimulus and the response are linked remains to be elucidated. We think it is quite likely that incompletely conditioned air penetrates into the intrathoracic airways with the depth being in direct proportion to the thermal conditions created by the magnitude of $\dot{V}_E$ and the degree to which Ti and Wi differ from body conditions. In a previous study we showed that the potentiation of the post-exercise obstructive response by cold air occurred despite complete cholinergic blockade, an observation which ruled out upper airway reflexes

as playing a role (2). In addition, in this study, we presented data that after vagal-efferent blockade the inhalation of cold air during exercise uniformly resulted in a fall in density dependence of maximum expiratory flow indicating that the predominant site of obstruction was in the peripheral airways. As a corollary, in preliminary experiments in which we recorded the temperature in the esophagus at the level of the carina in exercising asthmatics who were breathing subfreezing air, we found that esophageal temperature uniformly decreased as $\dot{V}_E$ rose.* Thus incompletely conditioned air penetrates well into the thorax, and hence a large thermal burden is likely placed on the subglottic airways which should result in direct cooling of their mucosa.

What then is the relationship between mucosal cooling and the development of bronchial obstruction? It seems likely that mediators of immediate hypersensitivity are involved since cromolyn sodium blunts the response (14,36). It is unknown as to how they are released, but there is a clinical precedent for cold causing the release of mediators from mast cells in the skin in cold urticaria (42). It is possible that a similar reaction occurs in the airway mucosa.

The next question for which we have no direct evidence one way or the other is whether asthmatics differ from normal subjects in being less able to condition inspired air, or whether their airways are simply more responsive to the effects of the thermal burden as they appear to be to other stimuli. However, the interaction between RHE, $\dot{V}_E$ and airway obstruction that we have explored herein provides new insights with which to begin to approach these problems.

* Deal, E.C., Jr., E. R. McFadden, Jr., R.H. Ingram Jr., and J.J. Jaeger (unpublished observations, 1978).

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LEGEND FOR FIGURES:

Figure 1. Schematic diagrahm of the apparatus employed in this study. The subjects inhaled through a heat exchanger which consisted of a heavily insulated, 76 cm-long copper tube with an internal diameter of 6.5 cm equipped with a 10.7 cm (ID) one-way valve on the inspiratory port. The temperature of the gas passing through the exchanger was regulated by varying the temperature of the fluid that was pumped from the thermal bath and circulated around the walls of the exchanger. Inspired air was brought to the desired water content by passing it through a bubble humidifier equipped with appropriate temperature controls. The air was then collected in a balloon reservoir before it entered the heat exchanger where excess moisture was permitted to "rain out" as the air cooled. A mixing valve permitted the addition of required amounts of CO_2 so as to keep end-tidal CO_2 measured at the mouth, at eucapnic levels. The desired level of ventilation was achieved by having the subjects keep a 7 Liter balloon (Target) that was in series with the expiratory port of the exchanger filled while it was being constantly evacuated through a flow meter by a vacuum source. The latter was equiped with electrical controls so that the rate of emptying of the balloon, and thus $\dot{V}_E$, could be varied at will. The position of the thermocouples are shown by the solid dots.

Figure 2: Changes that developed in one second forced expiratory volumes (FEV_1) of various levels of minute ventilation ($\dot{V}_E$) and inspired air conditions. The data points are mean values and the brackets represent one standard error of the mean. The symbols and numeric data in the insert represent the mean inspired air temperatures (Ti) and water contents (Wi) of the four air conditions employed in this study. The data points at the extreme left of the graph represent the effects of inhaling each gas mixture on lung function at rest as determined from previous studies in the same patients (1,3,4).

Figure 3: Changes that developed in specific conductance (SGaw) at various levels of minute ventilation ($\dot{V}_E$) and inspired air temperatures (Ti) and water contents (Wi). The format is identical to Figure 2.

Figure 4: Changes that developed in residual volume (RV) at various levels of minute ventilation ($\dot{V}_E$) and inspired air temperatures (Ti) and water contents (Wi). The format is identical to Figures 2 and 3.

TABLE 1

Experimental conditions during hyperventilation that simulate a heavy workload

	Subfreezing				Room Temp., Dry				Room Temp., Saturated				Body Temp., Saturated			
Subject	$\dot{V}_E$	Ti	Wi	$PetCO_2$	$\dot{V}_E$	Ti	Wi	$PetCO_2$	$\dot{V}_E$	Ti	Wi	$PetCO_2$	$\dot{V}_E$	Ti	Wi	$PetCO_2$
1	49.0	-11	0	36.2	48.4	24.5	0	39.0	48.9	23.0	20.5	37.3	48.4	37.0	44.0	34.3
2	77.4	-14	0	37.3	76.9	26.0	0	36.0	75.9	23.0	20.5	39.8	77.8	38.0	46.0	37.7
3	70.1	-12	0	38.0	70.5	23.0	0	37.6	70.8	23.0	20.5	36.4	71.4	36.0	42.0	36.6
4	52.0	- 9	0	38.2	53.2	23.5	0	32.8	56.0	23.0	20.5	37.3	52.4	37.5	45.0	34.7
5	44.4	-12	0	38.4	42.6	24.5	0	38.7	47.9	25.0	23.0	39.8	44.0	38.0	46.0	37.7
6	51.9	-13	0	37.4	63.3	24.0	0	36.6	60.1	23.0	20.5	36.5	55.8	36.0	42.0	37.3
7	73.6	-13	0	37.8	74.0	18.0	0	35.5	73.1	21.5	19.2	37.3	76.9	36.5	43.0	36.3
8	77.6	-13	0	38.1	77.0	23.0	0	36.3	77.7	23.0	20.5	35.2	77.8	37.5	45.0	36.2
MEAN	62.0	-12.1	0	37.7	63.3	23.3	0	36.6	63.8	23.1	20.7	37.5	63.1	37.1	44.1	36.4
SD	14.0	1.6	0	0.7	13.6	2.4	0	2.0	12.1	0.9	1.1	1.6	14.3	0.8	1.6	1.3

$\dot{V}_E$ = minute ventilation in L/min (BTPS); Ti = inspired air temperature in ^{o}C; Wi = inspired water content in mg H_2O/L air; $PetCO_2$ = partial pressure of end-tidal carbon dioxide in mm Hg.

The headings above each set of 4 columns refer to the individual experiments performed with various inspired air conditions.

TABLE 2

Experimental conditions during hyperventilation that simulate a moderate workload

Subject	Subfreezing				Room Temp., Dry				Room Temp., Saturated			
	$\dot{V}_E$	Ti	Wi	$PetCO_2$	$\dot{V}_E$	Ti	Wi	$PetCO_2$	$\dot{V}_E$	Ti	Wi	$PetCO_2$
1	31.1	- 9	0	38.0	33.9	23.5	0	38.8	34.4	23.5	20.9	38.8
2	52.5	-14	0	36.2	50.5	24.0	0	37.0	48.4	25.5	23.7	37.0
3	50.0	-12	0	35.4	50.0	25.0	0	37.1	48.9	23.0	20.5	37.1
4	39.8	-13	0	37.0	38.0	24.0	0	37.0	39.0	22.5	20.1	37.0
5	33.4	-11	0	39.5	33.6	21.0	0	37.5	32.9	24.0	21.5	37.5
6	41.6	-13	0	37.0	43.0	23.0	0	37.0	40.9	23.0	20.5	37.0
7	49.8	-14	0	36.8	48.4	24.0	0	36.7	48.6	23.5	23.7	36.7
8	55.9	-12	0	39.3	56.9	22.0	0	36.8	56.4	24.0	21.5	36.8
MEAN	44.5	-12.2	0	37.4	44.3	23.8	0	37.2	43.7	23.6	21.6	37.2
SD	8.8	1.7	0	1.4	8.5	1.3	0	0.7	8.2	0.9	1.4	0.7

$\dot{V}_E$ = minute ventilation in L/min (BTPS); Ti = inspired air temperature in ^oC; Wi = inspired water content in mg H_2O/L air; $PetCO_2$ = partial pressure of end-tidal carbon dioxide in mm Hg. The headings above each of the 4 columns refer to the individual experiments performed with various inspired air conditions.

TABLE 3

Changes in pulmonary mechanics following hyperpnea of 60 L/min while breathing dry air at subfreezing and room temperatures

	SUBFREEZING						ROOM TEMP., DRY					
	SGaw		FEV_1		RV		SGaw		FEV_1		RV	
Subject	B	R	B	R	B	R	B	R	B	R	B	R
1	0.17	0.07	3.37	2.72	1.42	1.81	0.24	0.17	3.42	3.05	1.51	1.61
2	0.15	0.06	3.63	2.05	1.29	2.55	0.15	0.06	3.65	2.44	1.99	2.97
3	0.12	0.03	2.32	1.09	1.46	2.99	0.14	0.04	2.75	1.27	1.14	1.69
4	0.14	0.02	2.55	1.22	1.13	2.53	0.20	0.04	2.77	1.81	1.19	1.79
5	0.16	0.03	3.39	2.08	1.69	2.26	0.14	0.04	3.28	2.66	1.85	1.89
6	0.11	0.02	2.09	0.98	1.75	3.28	0.14	0.03	2.20	1.31	1.50	2.83
7	0.15	0.05	2.67	1.85	1.59	2.67	0.14	0.07	2.57	2.14	1.36	2.24
8	0.11	0.04	3.92	3.02	2.79	3.16	0.13	0.06	3.63	2.98	2.70	2.90
MEAN	0.14	0.04	2.99	1.88	1.64	2.66	0.16	0.06	3.03	2.21	1.66	2.24
SD	0.02	0.02	0.67	0.75	0.51	0.49	0.04	0.05	0.54	0.70	0.51	0.53
p value	<0.001		<0.001		<0.001		<0.001		<0.001		<0.01	

Inspired air conditions in the subfreezing and room air experiments are listed in Table 1. SGaw = specific conductance in L/sec/cm H_2O/L; FEV_1 = one second forced expiratory volume in L; RV = residual volume in L; B = baseline; R = response observed post-hyperpnea. The p values were obtained from paired baseline-response comparisons.

TABLE 4

Changes in pulmonary mechanics following hyperpnea of 60 L/min while breathing fully saturated air at room and body temperatures

	Room Temp., Saturated						Body Temp., Saturated					
	SGaw		FEV_1		RV		SGaw		FEV_1		RV	
Subject	B	R	B	R	B	R	B	R	B	R	B	R
1	0.20	0.16	3.06	2.83	1.55	1.60	0.22	0.23	3.40	3.40	1.50	1.48
2	0.16	0.11	3.62	3.18	1.89	2.04	0.15	0.15	3.60	3.53	1.32	1.33
3	0.11	0.09	2.70	2.59	1.07	1.30	0.10	0.09	2.17	2.22	1.47	1.40
4	0.17	0.08	2.49	2.31	1.11	1.47	0.23	0.19	2.77	2.78	0.87	1.07
5	0.13	0.08	3.01	2.83	1.43	1.34	0.16	0.14	3.23	3.18	1.63	1.59
6	0.11	0.04	1.96	1.29	1.74	2.43	0.10	0.09	2.04	2.04	1.69	1.81
7	0.14	0.11	2.57	2.19	1.43	1.62	0.15	0.15	2.66	2.72	1.04	0.90
8	0.12	0.09	3.89	3.73	2.70	2.81	0.12	0.13	3.87	3.76	2.70	2.59
MEAN	0.14	0.10	2.91	2.62	1.62	1.83	0.15	0.15	2.97	2.94	1.53	1.52
SD	0.03	0.03	0.63	0.73	0.52	0.55	0.05	0.05	0.67	0.61	0.55	0.52
p values	<0.001		<0.005		<0.05		NS		NS		NS	

Inspired air conditions are given in Table 1. SGaw = specific conductance in L/sec/cmH_2O/L: FEV_1 = one second forced expiratory volume in L; RV = residual volume in L; B = baseline; R = response observed post-hyperpnea. The p values were obtained from paired baseline-response comparisons.

TABLE 5

Changes in pulmonary mechanics following hyperpnea of 40 L/min while breathing air at various conditions

	Subfreezing						Room Temp., Dry						Room Temp., Saturated					
	SGaw		FEV_1		RV		SGaw		FEV_1		RV		SGaw		FEV_1		RV	
Subject	B	R	B	R	B	R	B	R	B	R	B	R	B	R	B	R	B	R
1	0.20	0.14	3.16	2.92	1.48	1.81	0.20	0.14	2.90	2.81	1.73	1.79	0.20	0.17	3.14	2.86	1.46	1.60
2	0.20	0.14	3.42	3.00	1.29	1.42	0.15	0.10	3.63	3.35	1.74	1.94	0.17	0.16	3.40	3.20	2.03	2.12
3	0.11	0.05	2.22	1.70	1.35	1.72	0.14	0.09	2.61	2.35	1.09	1.17	0.14	0.11	2.64	2.51	1.11	1.21
4	0.19	0.09	2.43	1.98	1.04	1.29	0.19	0.15	2.51	2.23	1.15	1.35	0.19	0.16	2.58	2.42	1.17	1.18
5	0.13	0.05	3.01	2.73	1.43	1.52	0.13	0.07	3.03	2.86	1.50	1.44	0.13	0.08	3.14	3.04	1.65	1.48
6	0.09	0.02	1.80	1.12	1.82	2.87	0.09	0.04	1.94	1.68	2.11	2.81	0.11	0.07	2.03	1.98	1.69	1.85
7	0.16	0.11	3.16	2.65	1.19	1.56	0.18	0.14	3.01	2.96	0.99	1.16	0.17	0.19	2.84	2.94	1.36	1.40
8	0.16	0.10	3.95	3.74	2.75	2.96	0.16	0.13	3.82	3.70	2.68	2.87	0.16	0.14	4.01	3.91	2.99	3.08
MEAN	0.16	0.09	2.89	2.48	1.55	1.89	0.16	0.11	2.93	2.74	1.63	1.82	0.16	0.14	2.97	2.86	1.68	1.74
SD	0.04	0.05	0.70	0.83	0.54	0.65	0.04	0.04	0.60	0.64	0.57	0.69	0.03	0.04	0.60	0.58	0.61	0.63
p values	< 0.001		< 0.001		< 0.05		< 0.001		< 0.001		< 0.05		< 0.02		< 0.025		NS	

Inspired air conditions are listed in Table 2. SGaw = specific conductance in L/sec/cm H_2O L. FEV_1 = one second forced expiratory volume in L; RV = residual volume in L. B = baseline; R = response observed post-hyperpnea. The p values were obtained from paired baseline-response comparisons.

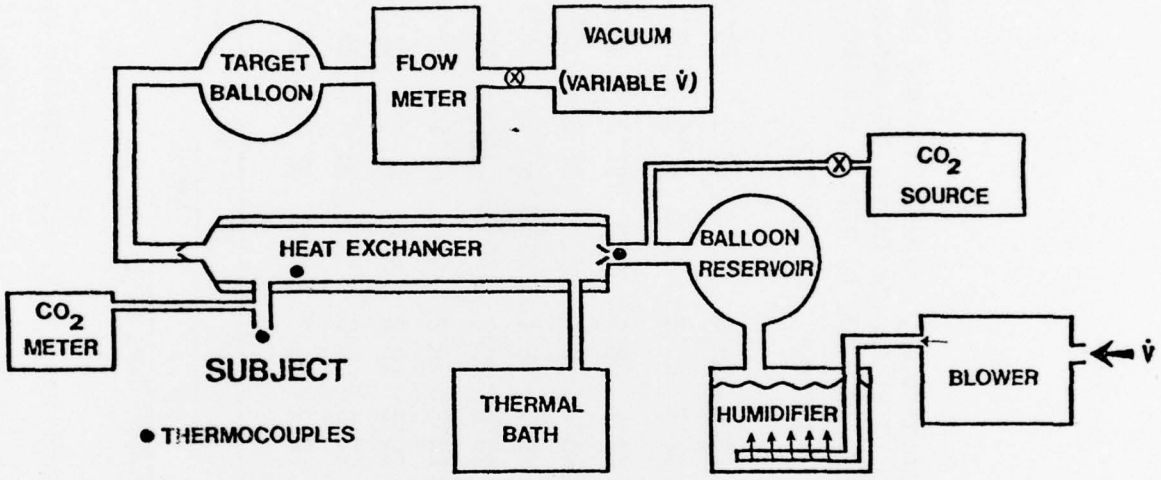

TARGET BALLOON
FLOW METER
VACUUM (VARIABLE V̇)
CO_2 SOURCE
HEAT EXCHANGER
BALLOON RESERVOIR
CO_2 METER
SUBJECT
THERMAL BATH
HUMIDIFIER
BLOWER
V̇
● THERMOCOUPLES

Fig 1.

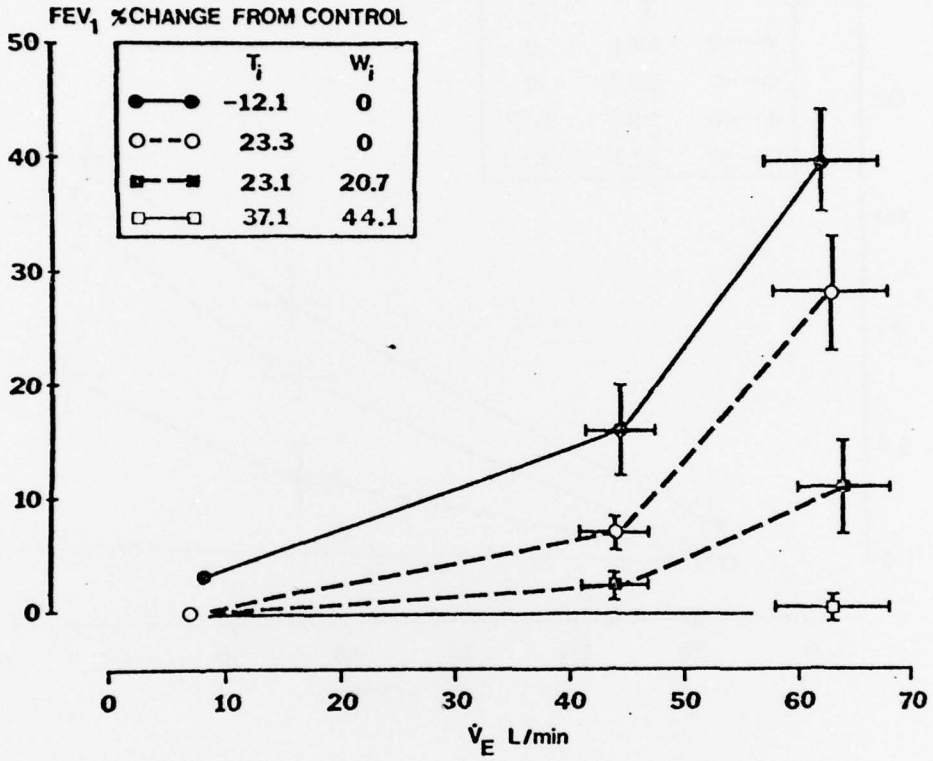

FEV1 %CHANGE FROM CONTROL
Ti
Wi
-12.1
0
23.3
0
23.1
20.7
37.1
44.1
50
40
30
20
10
0
0
10
20
30
40
50
60
70
V̇E L/min

Fig 2

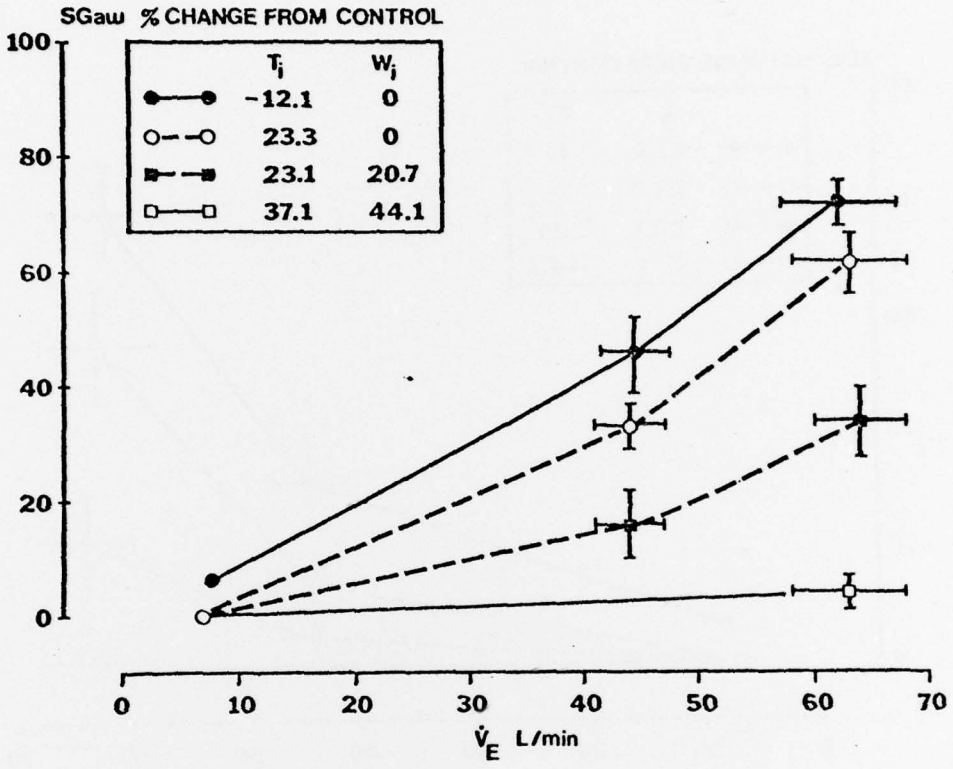
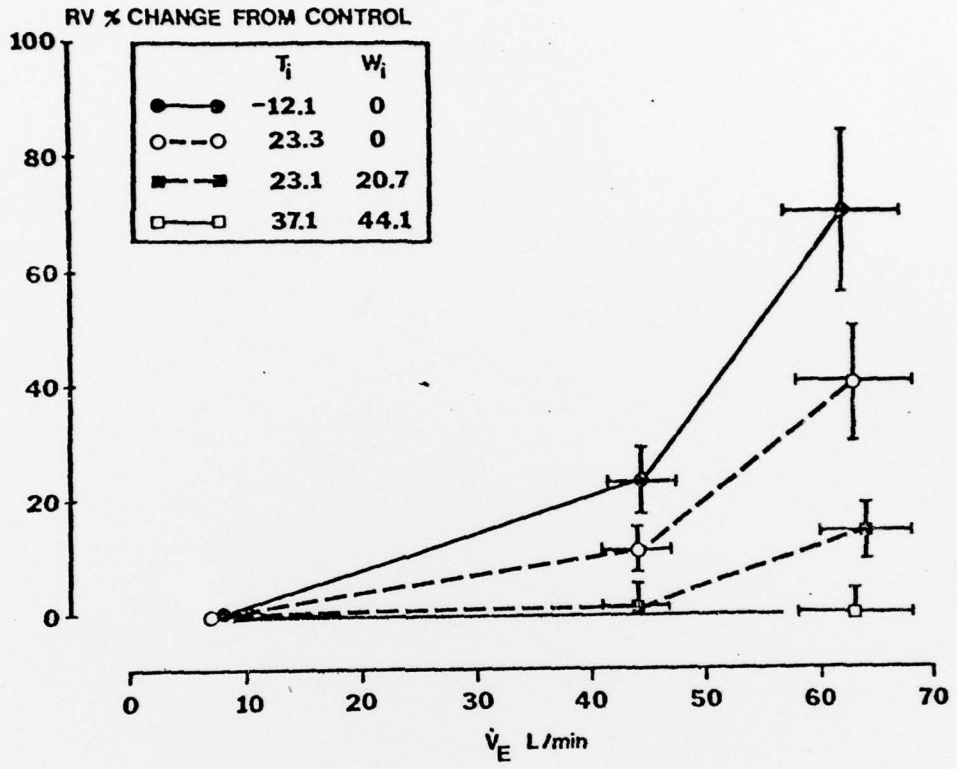

SGaw % CHANGE FROM CONTROL
100
80
60
40
20
0
T_i
W_i
-12.1
0
23.3
0
23.1
20.7
37.1
44.1
0
10
20
30
40
50
60
70
$\dot{V}_E$ L/min

Fig. 3


RV % CHANGE FROM CONTROL
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80
60
40
20
0
T_i
W_i
-12.1
0
23.3
0
23.1
20.7
37.1
44.1
0
10
20
30
40
50
60
70
$\dot{V}_E$ L/min

Fig. 4